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DATE MAILED: 12/28/95

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

☒ This application has been examined ☒ Responsive to communication filed on 8/7/95 ☐ This action is made final.

A shortened statutory period for response to this action is set to expire 3 month(s), ~~0~~ days from the date of this letter.
Failure to respond within the period for response will cause the application to become abandoned. 35 U.S.C. 133

Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

1. ☒ Notice of References Cited by Examiner, PTO-892.
2. ☒ Notice of Draftsman's Patent Drawing Review, PTO-948.
3. ☒ Notice of Art Cited by Applicant, PTO-1449.
4. ☐ Notice of Informal Patent Application, PTO-152.
5. ☐ Information on How to Effect Drawing Changes, PTO-1474.
6. ☐ _____.

Part II SUMMARY OF ACTION

1. ☒ Claims 1-24 are pending in the application.
   Of the above, claims 4, 7-12, 16, 19-24 are withdrawn from consideration.
2. ☐ Claims _____ have been cancelled.
3. ☐ Claims _____ are allowed.
4. ☒ Claims 1-3, 5, 6, 13-15, 17, 18 are rejected.
5. ☐ Claims _____ are objected to.
6. ☐ Claims _____ are subject to restriction or election requirement.
7. ☐ This application has been filed with informal drawings under 37 C.F.R. 1.85 which are acceptable for examination purposes.
8. ☐ Formal drawings are required in response to this Office action.
9. ☐ The corrected or substitute drawings have been received on _____. Under 37 C.F.R. 1.84 these drawings are ☐ acceptable; ☐ not acceptable (see explanation or Notice of Draftsman's Patent Drawing Review, PTO-948).
10. ☐ The proposed additional or substitute sheet(s) of drawings, filed on _____. has (have) been ☐ approved by the examiner; ☐ disapproved by the examiner (see explanation).
11. ☐ The proposed drawing correction, filed _____, has been ☐ approved; ☐ disapproved (see explanation).
12. ☐ Acknowledgement is made of the claim for priority under 35 U.S.C. 119. The certified copy has ☐ been received ☐ not been received ☐ been filed in parent application, serial no. _____; filed on _____.
13. ☐ Since this application apppears to be in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.
14. ☐ Other

PTOL-326 (Rev. 2/93)

EXAMINER'S ACTION

08 390 740

Part III DETAILED ACTION

Election/Restriction

1. Restriction to one of the following inventions is required under 35 U.S.C. 121:

Group I. Claim 1,2,3,5,6,13-15,17,18, drawn to recombinant DNA molecules comprising panec-1 and 2, expression vectors and host cells containing said nucleic acids, and diagnostic tests using said nucleic acids , classified in Class 435 , subclass 6, for example.

Group II. Claims 4 and 16, drawn to antisense DNA of panec-1 and panec-2, classified in Class 536, subclass 24.5.

Group III. Claims 7,8,19, and 20, drawn to a method of producing PANEC-1 and PANEC-2 polypeptides, and panec-1 and panec-2 polypeptides, classified in Class 530, subclass 350.1 for example.

Group IV. Claims 9-12, 21-24, drawn to antibodies, immunoassays, pharmaceutical compositions and methods of treatment, classified in Class 435, subclass 7.1, for example.

2. The inventions are distinct, each from the other because of the following reasons:

Inventions I,III and IV are disclosed as different combinations which are not connected in design, operation or effect. These combinations are independent if it can be shown that (1) they are not disclosed as capable of use together, (2) they have different modes of operation, (3) they have different functions, or (4) they have different effects. (MPEP 806.04, MPEP 808.01). In the instant case the combinations comprise products which are different in chemical and physical properties, means of isolation and use. The nucleic acids of Invention I may be used as probes, as sources of recombinant proteins, as reagents for antisense therapies and as reagents in gene therapies. The proteins of Invention III may be used as reagents in protein therapies or as immunogens in the generation of antibodies. The antibodies of Invention IV may be used in immunoassays or in antibody based therapies. The methods of Inventions I and IV are distinct in methods steps and outcome. Further the method of invention I does not make or use the products of invention IV. Although the method of invention II may use the product of invention I, (i.e nucleic acids may be used to generate recombinant protein), the products of Invention I as state above may be used in materially different processes.

Invention II is distinct from the Inventions of Group III and IV, in that the antisense nucleic acids of Invention II differ from the proteins and antibodies in biochemical and physical compositions as stated above.

Inventions I and II are drawn to different independent combinations; in that the nucleic acids of invention I, in addition to serving as a template for antisense DNA, may be used to generate genetic probes, as a source of recombinant proteins and as reagents for gene therapy. In contrast the antisense DNA, while useable as probes, may not serve as a source of recombinant protein, and additionally may be used as reagents in antisense gene therapies.

3. Because these inventions are distinct for the reasons given above and have acquired a separate status in the art as shown by their different classification, restriction for examination purposes as indicated is proper.

4. During a telephone conversation with Barbara J. Luther on Dec 14, 1995 a provisional election was made with traverse to prosecute the invention of Group I, claims 1-3,5,6, 13-15, 17 and 18. Affirmation of this election must be made by applicant in

responding to this Office action. Claims 4,7-12,16,19,20, and 21-24 are withdrawn from further consideration by the Examiner, 37 C.F.R. § 1.142(b), as being drawn to a non-elected invention.

5. Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 C.F.R. § 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a diligently-filed petition under 37 C.F.R. § 1.48(b) and by the fee required under 37 C.F.R. § 1.17(h).

Drawings

6. The drawings are objected to because Figures 1-3 contain sequences that are not indicated by a Seq. Id. No. thus failing to comply with 37 CFR 1.821 (c) Such seq. ID Nos. should be provided in the "Description of the Figures" on page 4. Correction is required.

Specification

7. The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The specification is objected to under 35 U.S.C. § 112, first paragraph, as failing to teach how to make and/or use the invention, ie. as failing to provide an enabling disclosure for a diagnostic test for activated or inflammatory conditions of the pancreas, and specifically for a diagnostic test for pancreatitis, employing panec-1 and panec-2 nucleic acid probes.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described in *In Re Colianni*, 195 USPQ 150 (CCPA 1977) and have been adopted by the Board of Patent Appeals and Interferences in *Ex Parte Forman*, 230 USPQ 546 (BPAI 1986). Among these factors are: the nature of the invention, the state of the prior art, the predictability or lack thereof in the art, the breadth of the claims, the amount of direction or guidance present, and the presence or absence of working examples.

A diagnostic test is claimed for activated or inflammatory conditions of the pancreas (such as pancreatitis). The test comprises the steps of providing a biological sample, combining

the biological sample with panec-1 or panec-2 nucleic acids. No additional steps are recited by which one extrapolates from detection to diagnosis.

The specification teaches the sequence of panec-1 and panec-2 and the prior art generically enables methods of ~~determining~~ performing hybridization assays using known nucleic acid sequences. However neither the art nor the specification teaches that the detection of panec-1 or panec-2 may be correlated with a disease state (the enablement required for a screening method) and provides no evidence that a change in panec 1 or panec-2 expression will provide an indicia of a particular disease state(s) (the enablement required for a diagnostic test). Therefore neither the specification nor the prior art enables the extrapolation from detection methods to a diagnostic test.

The specification and the art teaches that panec-1 and panec-2 share sequence homologies with chemokines and that the genes are expressed in the pancreas. The specification teaches that the genes are both "highly expressed" and "specifically expressed" in the pancreas although no data is presented to allow one to judge the parameters of this statement (what degree of expression constitutes "high" expression and more importantly does "specificity" imply that the panec genes are not expressed in other tissues?) .

The specification also teaches that :

"excessive expression of either PANEC-1 or PANEC-2 **can** lead to activation of monocytes, macrophages, basophils, eosinophils, T

lymphocytes and/or other cells which respond to chemokines by producing abundant proteases and other molecules which can lead to tissue damage or destruction. Therefor a diagnostic test for excess expression of PANECs **can** accelerate diagnosis and proper treatment of an abnormal condition caused by viral or bacterial infections: mechanical injury associated with trauma hereditary diseases affecting pancreatitis; biliary disease; infiltrative diseases such as leukemia and lymphomas; or other physiological and pathological problems which affect the function of the organ".

However it is not clear what the basis is for the assertion that excessive expression of PANEC 1 and 2 results in the variety of effects taught as no data is presented that the PANEC 1 and 2 products actually play a direct role in these processes; rather it appears that the role of PANEC 1 and 2 is assumed given that sequence homology indicates that the panec genes are chemokines and chemokines are known to play pleiotropic roles in the activation of the diverse cell types described and that the diverse pathologies recited are associated with changes in the levels of chemokines. It is further noted that the art teaches that chemokines are linked to complex signal transduction pathways and that the modulatory effects of chemokines are far from understood; i.e the art is unpredictable.

Further there is no guidance in the specification to allow one to determine what constitutes an abnormal deviation in levels of panec expression and therefore what differences in levels of expression are indicative of pathology. Although the specification teaches that upregulation of PANEC expression will be associated with pathology, there is no evidence provided that

this is so- as no teaching demonstrates that the pathologies listed are actually associated with panec misexpression. Since the sequences consisting of Seq IDs 1 and 3 as identified by the specification are novel, there are no analogous compounds in the prior art from which one might draw generic enablement for the claims. Given that the specification does not teach that the detection of panec-1 or panec-2 is correlated with a disease state (other than the assertion that this may be so) and provides no evidence that a change in panec 1 or panec-2 expression actually provides an indicia of a particular disease state(s) (again the specification only teaches that this is possible), the specification does not provide an adequate written description or sufficient enablement for a method of diagnosis of activated or inflammatory conditions of the pancreas and more specifically of pancreatitis.

Therefore it is the examiner's position that it would require undue experimentation for one to practice the methods of claims 2,3, 14 and 15.

Claim Rejections - 35 USC § 112

8. Claims 2,3,14 and 15 are rejected under 35 U.S.C. § 112, first paragraph, for the reasons set forth in the objection to the specification.

9. Claims 1,5,6, 13,17,18 are rejected under 35 U.S.C. § 112, first paragraph, as the disclosure is enabling only for claims limited to recombinant DNA molecules of defined sequence composition. See M.P.E.P. §§ 706.03(n) and 706.03(z).

The claims are drawn to recombinant DNA molecules comprising panec 1 or panec-2, to vectors comprising these DNA molecules and to host cells containing said vectors. The term "comprising" as recited in the claims is inclusive of any fragment or derivative of a nucleic acid which possesses the sole criteria that it includes the nucleic acid sequence shown in Seq. ID. No 1 and Seq ID No. 3. which the specification teaches is to encompass variants encoding the same or similar polypeptides, and active fragments. The specification has enabled the sequences of the panec -1 and panec-2 cDNAs. The specification while teaching that one **may** identify conservative variations in the protein without altering "function" of panec 1 and 2 has not actually taught variants or fragments of panec -1 and 2. The specification states that, encompassed by the meaning of the claims, are variants of PANEC 1 and PANEC 2 protein which maintain PANEC 1 and 2 functional activity. However this functional activity is not adequately enabled by the specification, which as stated above teaches speculated activities which may be associated with PANEC 1 and 2 but has not demonstrated how one may actually assay for PANEC 1 and 2 activity. It is therefor not clear what

specific role the PANEC 1 and 2 proteins play in the very complex genetic pathway of chemokines. Given that there is no clear guidance as to what measurable PANEC 1 and PANEC 2 activity is, it is unclear which variants of PANEC 1 and PANEC 2 would retain "functional activity" and therefore how one would use such variants. The specification, while teaching the structure of the cDNA does not provide any information about the genomic structure of panec-1 and panec-2. The language of the claims however clearly encompasses a genomic clone which is not enabled by the specification. As cited in Amgen Inc v. Chugai Pharmaceutical Co Ltd (18 USPQ2d, Nos 90-1273,-1275, 1991, CAFC), "Conception of chemical compounds requires that the inventor be able to define the compound so as to distinguish it from other materials, and to describe how to obtain it, rather than simply by defining it solely by its principle biological property; thus when inventor of a gene, which is a chemical compound, albeit a complex one, is unable to envision the detailed constitution of the gene so as to distinguish it from other materials, as well as the method of obtaining it, conception is not achieved until after reduction to practice has occurred and until after the gene has been isolated."

Further, citing Fiers v. Sugano (CAFC, 25 USPQ 2d, Nos 92-1170,-1171, 1993)," specification containing statements that claimed DNA sequence is part of the invention and reference to a potential method for isolating the sequence does not satisfy the

written description requirement of 35 USC 112, since the specification does not describe the DNA itself, nor even demonstrate that the disclosed method would actually produce the DNA in question."

Therefore in view of the unpredictability of the art with respect to variants and fragments and unspecified nucleic acids comprising the panec gene, and the unpredictability of isolating genomic clones and characterizing the structure of a gene, it is the position of the examiner that it would require undue experimentation for one of ordinary skill in the art to make and use the nucleic acids, expression vectors and host cells of the claims as broadly written.

Claim Rejections - 35 USC § 102

10. The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1,5,6, 13,17, and 18 are rejected under 35 U.S.C. § 102(b) as being anticipated by Caput et al. (EP 0488900-A, 03 June 1992, cited as Genbank Sequence Listing) over the broad language of the claims. Caput et al. teach a recombinant DNA

molecule "comprising" the sequence of Seq. ID. No. 1 as well as expression vectors and host cells comprising said sequence. The sequence taught is a "variant" of the panec-1 sequence. The same recombinant DNA molecule also "comprises" the DNA sequence of PANEC-2 and is a variant of the panec-2 sequence.

11. No claims are allowed.

12. Papers related to this application may be submitted to Group 1800 by facsimile transmission via the P.T.O. Fax Center located in Crystal Mall 1. The CM1 Fax Center number is (703) 305-7939. Please note that the faxing of such papers must conform with the notice to Comply published in the Official Gazette, 1096 OG 30 (Nov 15, 1989).

An inquiry regarding this communication should be directed to examiner Dianne Rees, Ph.D., whose telephone number is (703) 308-6565. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, W. Gary Jones, can be reached on (703) 308-1156.

Any inquiry of a general nature or relating to the status of the application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Dianne Rees
Dianne Rees
Dec 17, 1995

W. GARY JONES
SUPERVISORY PATENT EXAMINER
GROUP 1800
12/18/95